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Multiple Myeloma: A Patient With Unusual Features Including Intracranial and Meningeal Involvement, Testicular Involvement, Organomegaly, and Plasma Cell Leukemia

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A 27-year-old Chinese male presented with multiple myeloma. Over his 18-month course he manifested a number of unusual features of his disease including his young age, marked organomegaly, a testicular plasmacytoma, multiple intracranial extraskeletal plasmacytomas and meningeal involvement, and peripheral blood plasmacytosis. The case is described and recent literature on these rare manifestations is reviewed. Am. J. Hematol. 57:51–56, 1998. © 1998 Wiley-Liss, Inc.

Key words: multiple myeloma; plasma cells; meninges; testes; leukemia

INTRODUCTION

Multiple myeloma most commonly presents in middle-aged or elderly individuals. Frequent manifestations of multiple myeloma include lytic bone disease, renal involvement, hypercalcemia, anemia, and hyperviscosity. Spinal cord compression is the most common neurologic presentation. There are a number of other manifestations that have been described but occur rarely. We describe a patient whose course was complicated by several unusual complications including marked organomegaly, a testicular plasmacytoma, multiple intracranial extraskeletal plasmacytomas and meningeal involvement, and peripheral blood plasmacytosis. Recent literature on these features of multiple myeloma is reviewed.

CASE REPORT

JYH was a 27-year-old male who had recently arrived from China. He presented to Elmhurst Hospital Center in May 1994 with weakness, weight loss of 30 pounds over 2 months, and gingival bleeding. His past medical history, social history, and family history were unremarkable. Physical examination on presentation was notable for hepatosplenomegaly (liver edge palpated 5 cm below the right costal margin and spleen 4 cm below the left costal margin). Laboratory studies revealed: white blood cell count (WBC) 8,000/μl, hemoglobin (Hgb) 10 g/dl, hematocrit (Hct) 30%, platelet count 48,000/μl, prothrombin time (PT) 18.9 sec, activated partial thromboplastin time (APTT) 55 sec. The peripheral blood smear showed rare plasma cells. Additional coagulation studies included a fibrinogen of 167 mg/dl, a normal thrombin time, and negative fibrin degradation products. The factor X level was 38%. Serum creatinine and lactate dehydrogenase were normal and serum Ca^{++} was mildly decreased at 8.3 mg/dl. Serum protein electrophoresis revealed a total protein of 4.9 g/dl, albumin 3.0 g/dl, and gamma globulin of 0.9 g/dl. Quantitative immunoglobulin values were IgG 977 mg/dl (normal) and IgA and IgM low at 37 and 27 mg/dl. Serum immunoelectrophoresis demonstrated no abnormal intact immunoglobulin but an abnormal lambda chain. Urine protein electrophoresis revealed 86% gamma globulin, predominantly the same abnormal lambda chain as in the serum. Total urine protein was not quantified. Bone marrow aspiration and biopsy (Fig. 1a,b) revealed a hypercellular marrow with approximately 40% plasma cells, some of which had atypical nuclei. Immunostaining showed intracytoplas-

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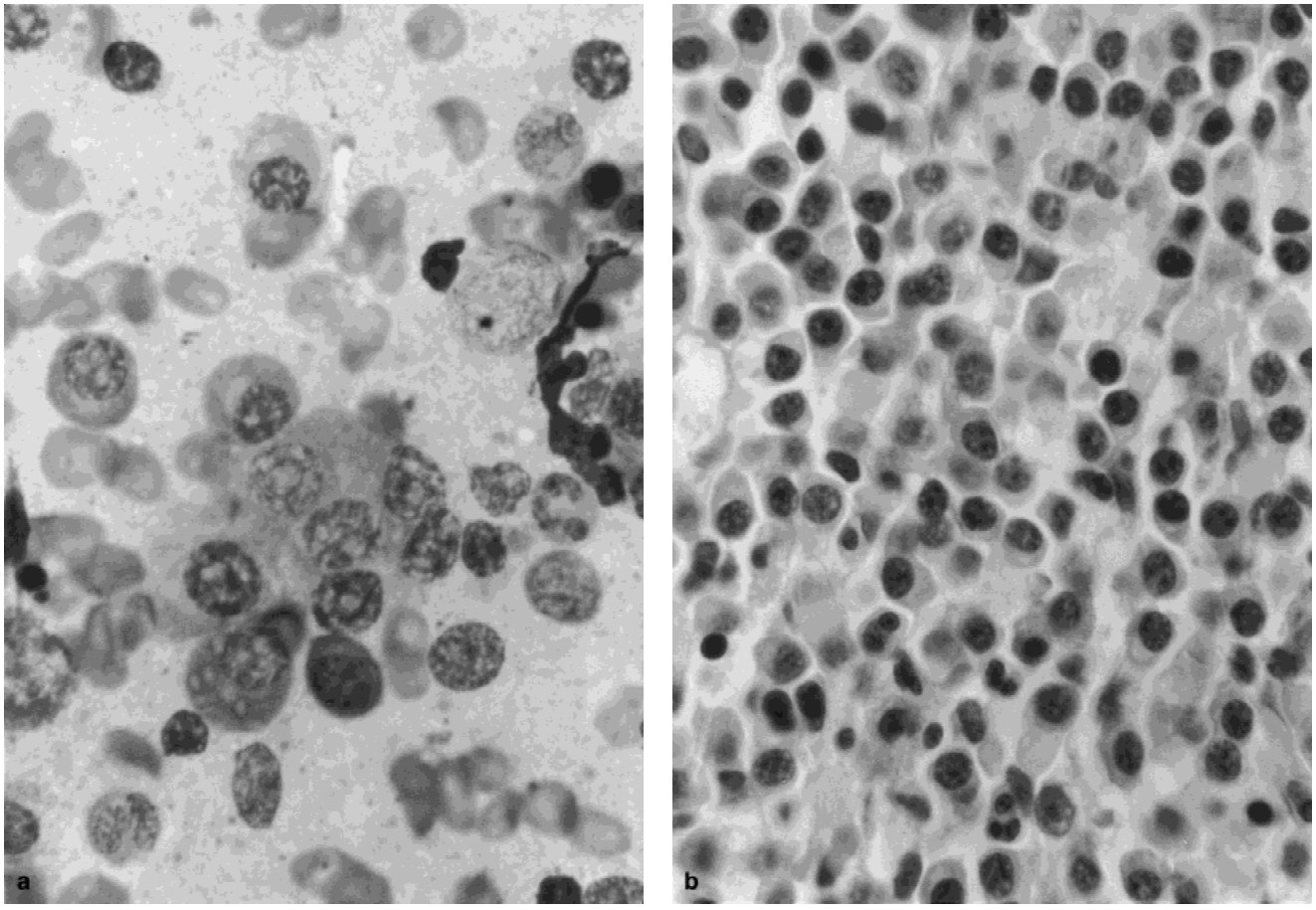

Fig. 1. a: Bone marrow aspirate showing vacuolated and multinuclear plasma cells (×1,000). b: Bone marrow biopsy (hematoxylin-eosin) showing many plasma cells (×200). All from presentation in May 1994.

mic gamma and lambda chains. Congo red and Toluidine blue stains were negative. A skeletal survey revealed no lytic or blastic lesions. The serum β_2-microglobulin level was 6.1 mg/L.

A diagnosis of multiple myeloma was made and the patient was begun on the M2 protocol (carmustine 20 mg/m^2 cyclophosphamide 400 mg/m^2, and vincristine 1.2 mg/m^2 intravenously, and melphalan 8 mg/m^2 and prednisone 40 mg/m^2 orally, every 4–5 weeks) [1,2]. After the first cycle, the plasma cells in the peripheral blood disappeared and the PT, APTT, and fibrinogen returned to normal within several days. The hepatosplenomegaly regressed and disappeared by late July. The anemia and thrombocytopenia resolved. By November 1994 the urine protein was only 200 mg/24 h (no UPEP done). His serum immunoglobulins were normal in February, 1995, with IgG 1,180 mg/dl, IgA 128 mg/dl, and IgM 46 mg/dl. No abnormal light chain was noted on serum immunofixation and the β_2-microglobulin level had decreased to 1 mg/L. He continued on the M2 protocol through March, 1995, receiving 10 cycles.

The patient was then lost to follow-up until July 1995. His CBC was normal but the urine revealed an abnormal lambda light chain on a concentrated specimen. He next presented in October 1995 with recurrence of anemia and thrombocytopenia and was noted to have a testicular mass, which was confirmed by ultrasound. His urine protein at that time was 7.6 g/24 h, with the protein consisting of the same abnormal lambda light chain. The β_2-microglobulin level had risen to 6 mg/L. Skeletal survey revealed small lytic lesions in the proximal humeri. Repeat bone marrow examination showed 75–80% infiltration with plasma cells. After consultation with the urology service, it was decided to treat his multiple myeloma and to biopsy the testicular mass only if it did not resolve. Clinical improvement was noted after the first cycle of M2, given at the same doses as during the initial therapy, and the testicular mass was no longer palpable.

On follow-up visit to the Hematology Clinic in late November he complained of recent onset of persistent headache and was noted to have papilledema. He was admitted to the hospital and a CT scan without contrast was performed, which was essentially unremarkable, but because of the papilledema and persistent symptoms, an MRI scan was performed (Fig. 2). This revealed extensive enhancing tumor within the base of the skull involv-

Fig. 2. MRI from December 1995; post-contrast T1 transaxial view that reveals enhancing lenticular-shaped homogeneous soft tissue masses along the anterior aspects of the middle cranial fossae bilaterally, which demonstrate extrinsic compression on the anterior aspects of the temporal lobes.

ing the body and greater wings of the sphenoid bone and clivus and with extension into the anterior aspects of the middle cranial fossae, the posterior aspect of the right orbit, the posterior cavernous sinuses, and the sphenoid and left posterior ethmoid sinuses. No definite lesions were seen in the brain parenchyma, suggesting that all the lesions were dural-based. Examination of the cerebrospinal fluid (CSF) revealed 378 WBC/μl, with 80% plasma cells (Fig. 3). The CSF protein was 42 mg/dl and the glucose was 65 mg/dl. Radiation Oncology was consulted and the patient was scheduled to receive 2,400 cGy in 12 fractions, but treatment had to be withheld after 4 fractions because of severe thrombocytopenia. A skeletal survey in mid-December showed multiple small lytic lesions in the humeri, the right scapula, the right femur, and both ischia. Urine protein on admission was 6 g/24 h and by late December it was 8.7 g/24 h, and plasmacytosis was present in the peripheral blood, at 4% on 12/13 and up to 28% on 12/22 (Fig. 4). At that time the peripheral blood smear also showed nucleated red blood cells and a marked left shift. Bilateral testicular involvement was demonstrated by ultrasound. Systemic chemotherapy was reinstituted, this time with doxorubicin 30 mg/m^2, carmustine 30 mg/m^2, vincristine 1.2 mg/m^2, and prednisone 60 mg/m^2. The patient rapidly became profoundly granulocytopenic, developed gram-negative sepsis unresponsive to antibiotics, and expired.

DISCUSSION

This patient manifested several unusual features of multiple myeloma, including his young age, marked hepatosplenomegaly, a testicular mass, and CNS involvement. With regard to age, the median age at diagnosis is 69 years, with more than 93% being 50 or older at diagnosis [3], but myeloma has been described in young men [4,5], usually with a long, indolent course in contrast to the rapid downhill course in this patient. Organomegaly is typically part of the POEMS syndrome [6], but this patient did not have other manifestations of that syndrome. Hepatomegaly was reported by Kyle and Bayrd [7] in half the patients with amyloid and myeloma, with splenomegaly in 10%, and a low factor X level has been associated with amyloid [8], but the negative Congo red stain on this patient's bone marrow and the rapid resolution of the hepatosplenomegaly [9] make amyloid unlikely. Another possible mechanism for the organomegaly in this patient is light chain deposition disease, in which monoclonal light chains that do not form fibrils or bind Congo red are deposited [10]. Response of this entity to therapy has not been described. There are a few recent case reports of hepatomegaly and/or splenomegaly in plasma cell dyscrasias without POEMS or amyloid, including two patients with primary splenic presentations who later progressed to generalized disease [11], a patient with multiple myeloma and splenomegaly that responded to intensive chemotherapy [12], a patient with multiple myeloma, massive splenomegaly, and peripheral blood and bone marrow changes compatible with agnogenic myeloid metaplasia, all of which resolved with treatment with M2 [13], and a man with multiple myeloma and hepatomegaly with multiple hypoechoic lesions in the liver, which were significantly reduced by chemotherapy for the myeloma [14].

Isolated plasmacytomas involving the testes and testicular involvement in multiple myeloma were reviewed by Oppenheim and colleagues in 1991 [15], and there have been only two case reports since then [16,17]. Although testicular tissue was not obtained from the present patient, the fact that his mass resolved after treatment and recurred as his monoclonal protein increased, suggests that the mass was a plasmacytoma.

The most common neurologic manifestations of multiple myeloma are spinal cord or nerve root compression by plasmacytomas arising from ribs or the epidural space

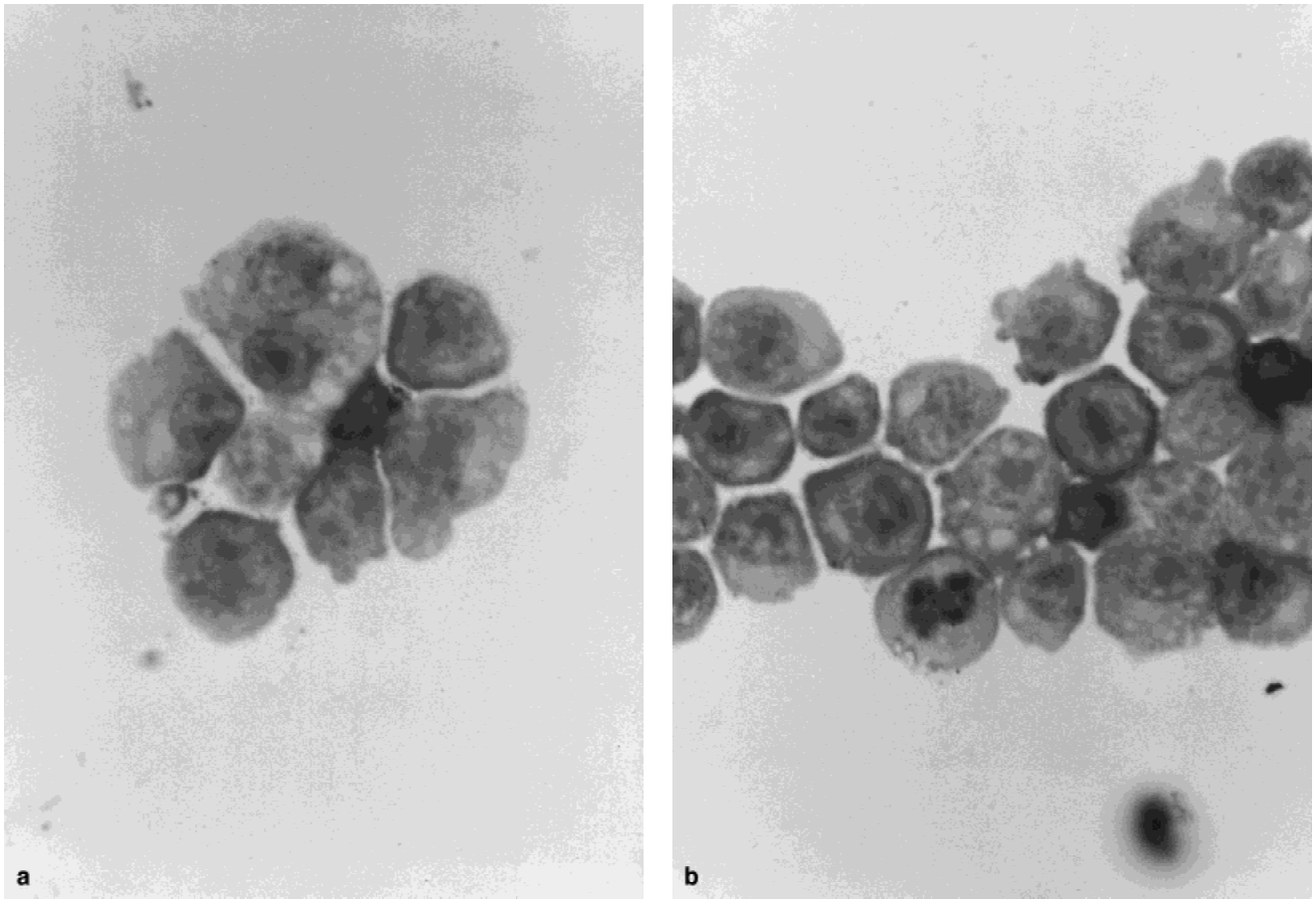

Fig. 3. Cerebral spinal fluid plasma cells, December 8, 1995. Panels a and b show two fields from the cytospin of the fluid.

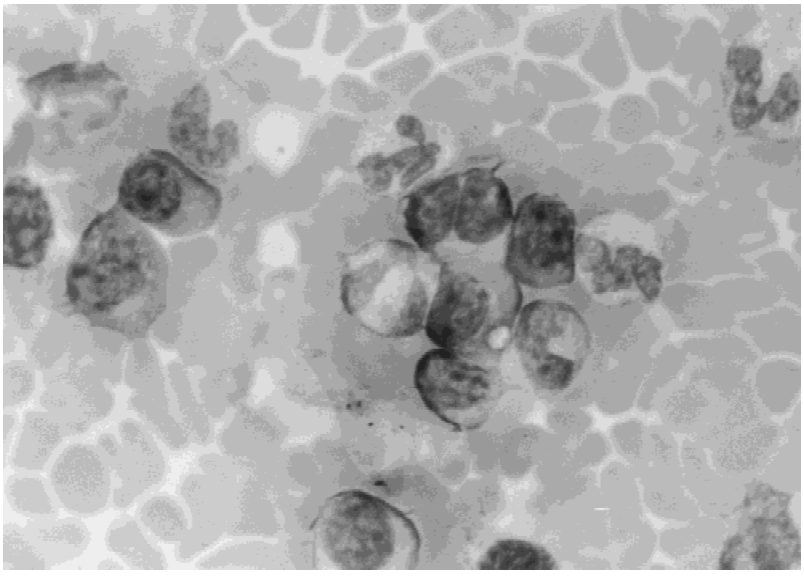

Fig. 4. Peripheral blood smear, December 22, 1995, showing several plasma cells as well as normal leukocytes.

and which occur in 10 to 20% of patients [18–25] and mental confusion secondary to hypercalcemia, which also occurs in 10 to 20% of patients [26]. Intracranial myeloma and myelomatous meningitis are very rare [27,28], and this has been suggested to be due to dural resistance to plasma cell invasion [29,30]. Since the advent of CT and MR scanning there have been several case reports of intracranial and/or meningeal involvement [31–39], with MR scanning reported to be more sensitive in most cases. The majority of the patients described in these reports had neurologic signs or symptoms. Although some had lytic lesions in the skull on plain film, others, like our patient, had normal skull films, and at surgery several patients with intracranial disease were noted to have no cranial involvement although most had dural involvement [34,37]. 99^{m}-Technetium-HMPAO SPECT scanning has also been reported to be able to detect intracranial myeloma [40].

Meningeal involvement by multiple myeloma is also rare. Leifer and colleagues reported three cases in 1992 (one of whom also had intracranial mass lesions) and found 34 cases in the literature [36]. More recently, cases were reported by Calavia et al. [41] (a patient with nonsecretory myeloma) and by Caminal et al. [42] (a patient with IgD myeloma and hyperammonemic encephalopathy). Nomoto et al. [43] described a patient with altered consciousness in whom an M protein was found in the CSF. Brain CT showed only a lesion of the temporal bone, but MRI revealed marked enhancement of the dura mater attributed to diffuse infiltration by malignant plasma cells. In 1996 Cavanna et al. [44] reported an additional case and noted the poor prognosis associated with meningeal involvement.

Our patient had both intracranial lesions and meningeal involvement. Because of the possibility of renal compromise by the CT contrast material, a noncontrast CT scan was performed that failed to show any masses, but MR scanning with gadolinium showed extensive enhancing tumor as described above. The lumbar puncture, performed after the MRI, showed plasma cells, confirming meningeal involvement as well as the intracranial mass lesions.

Because of the development of fatal Gram-negative sepsis, no attempt was made to treat the CNS disease specifically. Radiotherapy and surgery, alone or in combination have been used to treat intracranial mass lesions, with or without chemotherapy [34,39,45]. Intrathecal chemotherapy has been used in patients with meningeal involvement, but benefit, when it occurred, was short-lived [36,44].

The final unusual aspect of this case was the plasma cell leukemia (PCL) that was evident during the final admission, although he had in fact had a few peripheral blood plasma cells at initial presentation. PCL has been reported to occur in 0.5 to 5.6% [3,46–48] of myeloma patients and it makes up 0.2% of all leukemias [3]. It is associated with a poor prognosis, with a mean survival of less than 8 months [47] and a 5-year survival of 13% [3]. PCL is frequently the initial presentation of a plasma cell dyscrasia [49–53] or it may occur many years into the disease [54–56]. Our patient had a few peripheral blood plasma cells on presentation, which disappeared with successful treatment of his myeloma, but terminally he had a leukemic picture, with progression from 4 to 28% (4,000/μl) peripheral blood plasma cells over 9 days.

In summary, this young man, after an initial good response to chemotherapy, had a rapid downhill course and manifested several unusual features of his disease as described above. One wonders whether these features could have been explained by co-existent human immunodeficiency virus infection (HIV), which has been associated with rapid progression of other malignancies, particularly lymphomas. No risk factors for HIV were ascertained in his history, but because of the language and cultural barriers they could have been missed. The other question that arises is whether he should have received early myeloblative therapy and autologous stem cell or bone marrow transplant. He responded rapidly and apparently completely to the M2 regimen initially. The current literature [57] suggests that survival is improved with consolidation of therapy with transplantation and thus this patient might have benefited from that approach.

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